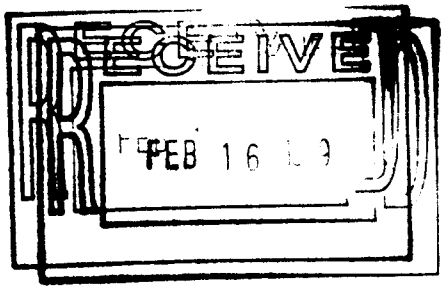
R.J. Reynolds Tobacco Company




MARY E. WARD
Senior Counsel
Research and Development

Winston-Salem, NC 27102
336-741-5376
Fax: 336-741-3763

February 15, 1999

C.W. Jameson, Ph.D.
National Toxicology Program
Report on Carcinogens
79 Alexander Drive, Room 3217
P.O. Box 12233
Research Triangle Park, NC 27709

Re: Ninth Report on Carcinogens
Environmental Tobacco Smoke (ETS)

Dear Dr. Jameson:

R.J. Reynolds Tobacco Company submits the enclosed written comments to the National Toxicology Program on its review of environmental tobacco smoke for listing in the *Report on Carcinogens*, Ninth Edition, as noticed in 63 Fed. Reg. 68783, December 14, 1998.

Sincerely,

Mary E. Ward
MEW:bb

Enclosure

Comments of the

# R. J. REYNOLDS TOBACCO COMPANY

on

*Listing of Environmental Tobacco Smoke*
*in the Report on Carcinogens, Ninth Edition*

by the

National Toxicology Program

February 15, 1999

W#793608.1

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## I. EXECUTIVE SUMMARY

NTP has not fulfilled its obligations to fairly and consistently consider environmental tobacco smoke ("ETS") for listing in its Ninth Report on Carcinogens. These comments show the following key deficiencies in NTP's review process and consideration of ETS:

- NTP's review of ETS was inconsistent with NTP's contemporaneous review of other substances;
- NTP failed to explain its inconsistent decisions and analyses concerning ETS as compared to other substances;
- NTP failed to apply consistent decision rules, and instituted policies and procedures that violate NTP's own obligations for reasoned decision-making in its listing decision on ETS;
- NTP failed to consider and evaluate dissenting opinions on NTP's own internal committees for ETS;
- NTP failed to conduct its own independent analysis of ETS and carcinogenicity;
- NTP based its conclusions regarding ETS on unreliable reports that have been vacated or superseded; and
- NTP failed to consider all relevant evidence placed in the record and failed to respond to issues raised in written comments and oral submissions.

## II. BACKGROUND

Substances being considered for listing in an NTP Report on Carcinogens go through a multi-level internal review process. After NTP's internal review process is complete, NTP must decide whether to list substances in its Report on Carcinogens. If NTP determines that the scientific evidence is sufficient to list a substance as a carcinogen, it has two options. A substance can be listed either as a "known human carcinogen" or as "reasonably anticipated to be a human carcinogen."

On December 2-3, 1998, the NTP's Board of Scientific Counselors ("BSC") met in Research Triangle Park, North Carolina to discuss its recommendations, as well as the recommendations of two internal NTP review committees (RG1 and RG2), for listing substances, including ETS, in the NTP Report on Carcinogens, Ninth Edition. At the meeting, the BSC recommended listing ETS as a "known human carcinogen." NTP had previously released a document titled "Draft Report on Carcinogens Background Document for Environmental Tobacco Smoke, December 2-3, 1998" (the "1998 ETS Draft"). The 1998 ETS Draft purports to address the following topics: Physical and Chemical Properties, Human Exposure, Studies of Cancer in Experimental Animals, Genotoxicity, Mechanistic and Relevant Studies, and References. By Federal Register notice, NTP solicited final public comments on ETS and additional agents, substances, mixtures, and exposure circumstances for listing in, or delisting from, the Report on Carcinogens, Ninth Edition. Reynolds submits these comments on the proposed listing of ETS as a "known human carcinogen" in the NTP's Report on Carcinogens, Ninth Edition and on the 1998 ETS Draft.[1]

[1]In response to previous Federal Register notices, Reynolds submitted written comments to NTP concerning ETS. Those comments are incorporated herein by reference. Reynolds' comments presented here address some, but not all, of the inconsistencies or unfairness in NTP's review process for its consideration of substances, such as ETS, for listing as a "known human carcinogen" or "reasonably anticipated to be a human carcinogen." In addition, Reynolds identifies new issues and information not considered or addressed in the 1998 ETS Draft. The NTP should not infer that the absence of comment on other issues presented in the 1998 ETS Draft implies Reynolds' acceptance of, or agreement with, the conclusions reached, or data reported, by NTP.

## III. NTP'S DETERMINATION TO LIST ETS AS "KNOWN TO BE A HUMAN CARCINOGEN" IS ARBITRARY BECAUSE OF NTP'S FAILURE TO APPLY REASONED STANDARDS TO THE EVIDENCE.

Although the exercise of expert discretion is the lifeblood of an administrative agency, the standardless exercise of that discretion is unlawful.[2] Judicial review under the Administrative Procedure Act prevents agencies from engaging in unreasoned decision making:

> Courts require that administrative agencies articulate the criteria employed in reaching their result and are no longer content with bare administrative *ipse dixits* based on supposed administrative expertise. While an agency may have discretion to decide, discretion does not include a right to act perfunctorily or arbitrarily; and, in order for a Court to make a critical evaluation of the agency's action and to determine whether it acted perfunctorily or arbitrarily, the agency must in its decision explicate fully its course of inquiry, its analysis and its reasoning.

*Appalachian Power Co. v. EPA*, 477 F.2d 495, 507 (4th Cir. 1973) (citations and quotations omitted). NTP's determination to list ETS as a "known human carcinogen" is precisely the type of rudderless voyage that the Administrative Procedure Act prohibits.[3]

Section 301(b)(4)(A)(*i*) of the Public Health Service Act requires a list of all substances which either are known to be carcinogens [in humans] or may reasonably be anticipated to be

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[2]"There are no findings and no analysis here to justify the choice made, no indication of the basis on which the agency exercised its expert discretion. We are not prepared to and the Administrative Procedure Act will not permit us to accept such practice. Expert discretion is the lifeblood of the administrative process but 'unless we make the requirements for administrative action strict and demanding, expertise, the strength of modern government, can become a monster which rules with no practical limits on its discretion.'" *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm*, 463 U.S. 29, 103 S.Ct. 2856 (1983) (*quoting*, *Burlington Truck Lines v. United States*, 371 U.S. 156, 167 (1962)).

[3]NTP decisions are reviewable under the Administrative Procedure Act. *SOCMA v. Secretary, Department of Health and Human Services*, 720 F. Supp. 1244 (W.D. La. 1989).

[human] carcinogens. The Eighth Report on Carcinogens recently listed substances in the following categories:

> Known to be a Human Carcinogen:
> There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.
>
> Reasonably Anticipated to be a Human Carcinogen:
> There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding factors, could not adequately be excluded.

These criteria are neither self-explanatory nor self-executing. NTP must explain what constitutes "sufficient evidence of carcinogenicity in humans" and how the record satisfies that standard before listing a substance as a "known human carcinogen." Mere conclusory assertions that these standards have been met in listing decisions will not suffice. Rather, the agency must, at a minimum, answer a number of questions. What is the test of sufficiency? What specific standards must the data satisfy? How do we determine whether the data satisfy the standards? On these questions, the BSC conceded that it did not have a clue, especially when it came to evaluating ETS.

Dr. Mirer, a member of the BSC, recognized the lack of consistency in NTP's assessment of the carcinogenicity of substances considered for listing in the Ninth Report on Carcinogens. During Dr. Mirer's comments the following exchange took place:

> Dr. Mirer: Well, yeah. The conclusion is that if we are -- I think if we are following consistent decision rules here, which we are obviously not, but if we were to follow consistent decision rules, I think we would have—
>
> Dr. Hooper: (interposing) We don't have any decision rules.
>
> Dr. Mirer: What?
>
> Dr. Hooper: We don't have any decision rules.

[BSC Tr. At 418-419, emphasis added]

Recognizing the lack of a consistent approach for evaluating epidemiological data, Dr. Hooper commented on the need for a set of NTP decision criteria for epidemiology:

> "[T]o me this points up the definite need for these – a decision criteria for epidemiology, the exchange between Dr. Bingham and Dr. Zahm. I think that both these are important but it can be resolved by having criteria that you make these decisions upon." [BSC Tr. at 424]

During the closing remarks from the BSC meeting, Dr. Hooper again emphasized the need to develop standards that can be consistently applied to all substances:

> "And what I would like to help me in that would be to set up criteria that I could start to fit epi studies or short term studies or animal data in terms of stratifying them as to satisfying certain criteria that is positive or negative. So in particular epi data needs to be structured so we have a decision criteria for it."

[BSC Tr. at 558].

In addition to requiring agencies to articulate both the standards and the basis for its decision criteria, the courts have defined the following types of conduct to be unreasoned decision making:

> Disregard of Evidence or Comments: Agencies cannot ignore challenges to their methodologies, assumptions, or decisions.[4]
>
> Unexplained Deviation from Prior Practices: Agencies must explain departures from established testing methods, assumptions or policies or decisions that seemingly treat similar situations differently.[5]

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[4]*See, e.g., Motor Vehicle Mfrs. Ass'n. of U.S. Inc. v. State Farm*, 463 U.S. 29, 43, 103 S.Ct. 2856, 2866 (1983) (holding that agency action is arbitrary and capricious if the agency has "entirely failed to consider an important aspect of the problem"); *American Mining Congress v. United States EPA*, 907 F.2d 1179, 1188-89 (D.C. Cir. 1990) (setting aside EPA's decision to classify wastes as "hazardous" because EPA failed to respond adequately to commented challenges to the EPA's testing data).

[5]*See, e.g., Western States Petroleum Ass'n v. EPA*, 87 F.3d 280, 284 (9th Cir. 1996) (reversing because "EPA must clearly set forth the grounds for its departure from prior norms"); *Transactive Corp. v. United States*, 91 F.3d 232, 237 (D.C. Cir. 1996) (agency action is arbitrary

Conclusory or Implausible Explanations: When an agency explains why it is rejecting commenters' evidence or its own established practices, its reasoning cannot be conclusory or implausible.[6]

As demonstrated below, NTP has engaged in all three of these impermissible types of conduct. NTP has failed to fulfill its obligations under the Administrative Procedure Act. NTP has exercised unlawful standardless discretion. NTP has disregarded scientific evidence that contradicts its conclusions. NTP without explanation inconsistently treats substances being considered for listing in its Ninth Report on Carcinogens. NTP has offered conclusory explanations in attempting to justify its rejection of evidence in the administrative record that is directly contrary to the evidence used to support its listing decision.

## IV. NTP'S ANALYSIS AND CONCLUSIONS REGARDING ETS ARE INCONSISTENT WITH NTP'S CONTEMPORANEOUS REVIEW OF OTHER SUBSTANCES.

It is axiomatic that NTP's review process must comprehensively address the record evidence and apply consistently reasoned decision standards to every substance being considered for listing in its Reports on Carcinogens. With respect to ETS, NTP failed on both counts. A close examination of NTP's review of ETS and carcinogenicity demonstrates that NTP failed to (1) fully and completely evaluate the evidence concerning ETS and carcinogenicity and (2) consistently apply decision rules to its listing determination.

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when the agency offer[s] insufficient reasons for treating similar situations differently).

[6]*See, e.g.*, *State Farm*, 463 U.S. at 43, 103 S. Ct at 2866 (holding that an agency explanation must be rejected if it "runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise"); *Millard Refrigerated Serv. Inc. v. FAA*, 98 F.3d 1361, 1363 (D.C. Cir. 1996) (rejecting an FAA explanation because it seemed "facially implausible").

### A. NTP's review of diesel exhaust is inconsistent with NTP's review of ETS.

The BSC recommended listing diesel exhaust particulates ("diesel exhaust") as "reasonably anticipated to be a human carcinogen." The BSC was not satisfied that the evidence was strong enough to recommend listing diesel exhaust as a "known human carcinogen." In contrast, when confronted with similar and often weaker evidence on ETS, the BSC recommended listing ETS as a "known human carcinogen." The evidence considered by NTP and comments of the members of the BSC demonstrate that NTP applied inconsistent scientific standards in evaluating ETS and diesel exhaust. If NTP had used the same scientific standards and reasoning in evaluating ETS that it used for diesel exhaust, the BSC would have recommended ETS for a less definitive, not more definitive, listing designation than for diesel exhaust.

#### 1. NTP inconsistently evaluated the chemistry and physics of ETS and diesel exhaust

Members of the BSC, including Dr. Bingham, stated they were impressed by the similarity of chemical constituents of diesel exhaust and ETS:

> One of the things that is impressive to me in the diesel is that you have the same kind of compounds. Let's say the fingerprint is not the same, but it's the same fingerprint that you have for other particulate PNA mixtures, complex mixtures that are potent carcinogens for humans.

[BSC Tr. at 420].

NTP identified some similarities in the "Draft Report on Carcinogens Background Document for Diesel Exhaust Particulates, December 2-3, 1998" (the "1998 Diesel Draft") and the 1998 ETS Draft. In particular, identically titled chapters in both 1998 Drafts state that ETS and diesel exhaust are aerosols that are products of organic substance combustion and are complex chemical mixtures of gases and particles. [1998 ETS Draft, p. 1; 1998 Diesel Draft, p. 1]. NTP claimed that diesel

exhaust and ETS contain many of the same compounds. [1998 ETS Draft App. 1, pp. 80-92; 1998 Diesel Draft, App. A-1].

Although NTP claims that ETS and diesel exhaust are chemically similar, the NTP Background documents on ETS and diesel exhaust take substantially different approaches in analyzing the chemical composition of these two aerosols.

First, and most important, the 1998 ETS Draft makes the egregious error of physically and chemically characterizing the wrong species. That is, whereas the 1998 Diesel Draft appropriately addresses the physical and chemical properties of diesel exhaust, the 1998 ETS Draft erroneously ascribes the physical and chemical properties of mainstream[7] smoke (MS) and sidestream[8] smoke (SS) to ETS.[9]

ETS is defined as the combination of aged and diluted SS (approximately 85%) and aged, diluted and exhaled MS (approximately 15%). It results from the rapid dissipation in room air of SS and exhaled MS smoke. As a result of the profound chemical and physical changes occurring during this aging process (e.g., cooling, evaporation, sedimentation, surface adsorption and

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[7]MS is the smoke - particulate and vapor phases - drawn through the tobacco rod, and inhaled by the smoker during smoking.

[8]SS is the combination of: 1) smoke emanating from the lit end of a cigarette during the smolder period between puffs; and 2) the smoke emanating from the lit end of a cigarette during the puff, including vapor phase constituents diffusing through the cigarette paper.

[9]Because mainstream, sidestream, and ETS are products of tobacco combustion, NTP implicitly accepts the false premise that the three species are identical or inconsequentially different. This notion is scientifically naive and methodologically reckless. It ignores the complex physical and chemical processes that differentiate the formation and evolution of the three distinct aerosol mixtures. As a direct consequence of this fundamentally erroneous premise, the entire 1998 ETS Draft chapter on physical and chemical properties is little better than irrelevant.

desorption and chemical reaction), ETS is chemically and physically distinct from both SS and MS.

The following table illustrates several important differences between ETS and SS.

| Property | Sidestream Smoke (SS) | Environmental Tobacco Smoke (ETS) |
|---|---|---|
| Particle Size (MMAD) | ~0.3 - 0.4 μm | ~0.15 - 0.2 μm |
| Particle Concentration | 1 - 5 million μg/m3 | 5 - 200 μg/m3 |
| Nicotine | Distributed between particle and vapor phases | Almost exclusively (~97%) in the vapor phase |
| Composition | Water and many volatile compounds distributed between particle and vapor phases | Water and many volatile compounds are in the vapor phase |
| Temperature | 600° C (1100° F) | 22 °C (72° F) |

Given the important physical and chemical differences outlined in this table, and especially the thousands to hundreds of thousands-fold differences in concentrations, it is obvious that the potential (even the probability) for biological differences between SS and ETS is great.

When considering ETS, NTP focused on the analysis of individual constituents of MS and SS and their reported carcinogenicity. In the ETS Draft, NTP provides a table of some of the constituents of MS and SS and their IARC carcinogenicity classifications. [1998 ETS Draft, pp. 4-8; Table 1-2]. With respect to diesel exhaust, however, the BSC eschews its constituent-by-constituent approach and makes no reference to IARC classification of diesel exhaust constituents -- despite the fact that at least 18 of the MS/SS constituents classified by IARC are also found in diesel exhaust. Instead, the 1998 Diesel Draft lists more than 300 chemical constituents, but does not in any way note whether those constituents of diesel exhaust have been identified as either chemical carcinogens or toxicants.

At least 24 constituents of mainstream and sidestream smokes that are listed by NTP are also

listed as constituents of diesel exhaust. [Appendix A-1, 1998 Diesel Draft].

| List of Chemical Constituents common to Diesel Exhaust and Mainstream/Sidestream Tobacco Smoke | |
|---|---|
| Carbon Monoxide | 1,3 Butadiene $C_4H_6$ |
| Hydrogen Cyanide | Benzo[b]fluoranthene $C_{20}H_{12}$ |
| Nitrogen oxides | Benzo[j]fluoranthene $C_{20}H_{12}$ |
| Nitric oxide | Benzo[k]fluoranthene $C_{20}H_{12}$ |
| Benzene | Chrysene $C_{18}H_{12}$ |
| Fluoranthene | Dibenz[a, j]anthracene $C_{21}H_{13}N$ |
| Phenol | Formaldehyde $CH_20$ |
| Benz[a]anthracene | Indeno[1, 2, 3-cd]pyrene $C_{22}H_{12}$ |
| Cadmium | Styrene $C_8H_8$ |
| Nickel | Arsenic As |
| Acetaldehyde $C_2H_4O$ | Chromium VI |
| Benz[a]anthracene | Lead [Pb] |

[1998 ETS Draft, Table 1-1, pp. 1-8 (tobacco smoke); 1998 Diesel Draft, Appendix A-1 (diesel exhaust)].

Despite the chemical similarities between MS/SS and diesel exhaust, NTP chose to apply different standards and methodologies to their analyses of the chemical and physical properties of MS/SS and diesel exhaust, respectively. NTP totally failed to consider the properties of ETS.

**2. NTP inconsistently evaluated the epidemiological studies of ETS and diesel exhaust**

Dr. Mirer candidly described the extremely liberal interpretation that NTP gave the ETS epidemiology as compared to NTP's rigorous interpretation of the diesel exhaust epidemiology:

> "I hope when we get to diesel we will get the same generous interpretation of epidemiology that we are getting here." [BSC Tr. at 239].

The "generous interpretation of epidemiology" to which Dr. Mirer was referring was the BSC's loose interpretation of epidemiological standards in its evaluation of ETS.

**a. NTP inconsistently evaluated the magnitude of the relative risks**

NTP's Dr. Kamel characterized the diesel exhaust epidemiological relative risks as "a relatively small elevation in risk." He described the ranges of reported risks for diesel exhaust: from 1.2 to 2.9, with most being in the 1.3 to 1.5 range, and a recent meta-analysis producing a summary risk of 1.33. [BSC Tr. at 379]. Largely on the basis of these very small reported and computed relative risks, the BSC recommended that diesel exhaust be listed as "reasonably anticipated to be a human carcinogen."

In contrast, the magnitudes of the relative risks reported by NTP were smaller than those reported for diesel exhaust. Dr. Bucher cited the following ETS relative risks: 1) EPA's meta-analysis summary odds ratio of 1.19 [BSC Tr. at 173]; 2) Fontham 1994's spousal odds ratio of 1.29 [BSC Tr. at 176]; 3) Stockwell 1992's spousal odds ratio of 1.60 [BSC Tr. at 176]; 4) Brownson 1992's spousal odds ratio of 1.0 [BSC Tr. at 176]; and 5) IARC 1998 odds ratios of 1.16 and 1.11 [BSC Tr. at 176]. Dr. Bucher recognized that the ETS and lung cancer odds ratios are "bouncing right around 1.15, 1.2, 1.25." [BSC Tr. at 179]. Dr. Zahm explained that relative risks of this magnitude are exceedingly weak and at the outer limits of what epidemiology is designed to be able to detect:

> "[I]ncreased risks of 20 percent are extremely difficult to establish as causal associations in epidemiological research." [BSC Tr. at 181].

Dr. Mirer compared the level of evidence between ETS and diesel exhaust: "I think it is clear that we would have to give this [diesel exhaust] the same level of evidence as environmental tobacco

smoke." [BSC Tr. at 418-419]. Despite such clear indications of similar or weaker epidemiological evidence, the BSC found the epidemiology research sufficient to recommend listing ETS as a "known human carcinogen."

**b. NTP recognized that the epidemiological relative risks for diesel exhaust studies are more consistent than the results for the ETS studies**

Several members of the BSC recognized that the diesel exhaust epidemiological data were more consistent than the data on ETS:

> "I looked at the consistency and was very impressed by diesel. You are right; it [the diesel epidemiology] is actually more consistent than it is for environmental tobacco smoke." [BSC Tr. at 419 (Dr. Zahm)].

With respect to the diesel exhaust studies, Dr. Zahm continued, "There is this consistency across studies which is really remarkable, this consistent lung cancer that is across the studies." [BSC Tr. at 389]. Dr. Mirer stated that "we have consistency across all of these groups." [BSC Tr. at 416]. Dr. Kamel noted that "three of three cohort studies and four of five case-control studies of diesel exhaust and lung cancer found [a statistically significant] association." [BSC Tr. at 379].

By comparison, the epidemiological data on ETS are inconsistent:

- Fully 20% of the worldwide ETS and lung cancer epidemiologic studies report relative risks of 1.0 or lower.
- Only one of the 15 U.S. ETS and lung cancer epidemiological studies cited in the 1998 ETS Draft found a statistically significant association. [1998 ETS Draft, p. 26] In other words, 14 of 15 U.S. studies of ETS and lung cancer did <u>not</u> find a statistically significant association.
- Among the four largest ETS and lung cancer epidemiological studies, one is significantly decreased (Wu-Williams 1990), one is precisely neutral (Brownson 1992), one is significantly elevated (Fontham 1994), and the most recent study does not reach statistical significance (IARC 1998).

- The studies published prior to 1990 yield a significant relative risk of 1.37, but the studies published since then yield a statistically nonsignificant 1.08.

[Stephen B. Sears, Ph.D. 1998 Written Submission to NTP].

**c. NTP inconsistently evaluated confounding in epidemiological studies of ETS and diesel exhaust**

In concluding that diesel exhaust should be listed as "reasonably anticipated to be a human carcinogen," NTP specifically recognized the difficulty of adequately controlling for confounding given the weakness of the reported associations. [BSC Tr. at 389]. For example, in responding to Dr. Kamel's recommendation that the BSC list diesel exhaust as a "known human carcinogen,"[10] the primary reviewer for the 1998 Diesel Draft (Dr. Zahm) explained her difficulties in supporting such a conclusion because of the inherent problems of confounding in interpreting low-level relative risks found in the diesel epidemiology. [BSC Tr. at 388-390].

With respect to the ETS epidemiological literature, the BSC summarily dismissed the well-documented problems of confounding and bias without discussion.[11] Numerous written and oral presentations to the BSC documented the presence of confounding and bias in the ETS epidemiological studies. Yet Dr. Zahm stated conclusorily that the recent studies had adequately controlled for confounding and bias. [BSC Tr. at 183-184]. NTP has offered no explanation for the

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[10]Regarding diesel exhaust, Dr. Kamel stated: "In humans, lung cancer is found consistently in occupational groups exposed to diesel exhaust. Even though this is a relatively weak effect, there are some reasons to believe that the association is causal. For example, it is consistently found across many studies, exposure response relationships have been detected, and there is evidence that the relationship - that the association is not due to confounding." [BSC Tr. at 383]

[11]Dr. Geoffrey Kabat, a member of the EPA ETS Science Advisory Board that reviewed EPA 1992, concluded that confounding could not be ruled out as an explanation for any observed association in the ETS and lung cancer epidemiological studies. (Koo and Kabat *et al.*, 1997).

inconsistent treatment of this fundamental issue in interpreting epidemiology.

The BSC determined that the data on diesel exhaust were unconvincing because of the weakness of the epidemiological risks and inherent problems of confounding and bias. With respect to ETS, the BSC did not apply the same scientific standards that it applied to diesel exhaust. For ETS, the BSC did not demand that the epidemiological data be consistent and convincing before recommending listing ETS as a "known human carcinogen."

### 3. NTP recognized that studies of cancer in experimental animals are generally positive for diesel exhaust, but negative for ETS

Dr. Kamel stated unequivocally that "diesel exhaust has also been shown to cause cancer in animals. For example, inhalation of whole diesel exhaust consistently produced lung tumors in rats and sometimes mice." [BSC Tr. at 381]. Dr. Zahm agreed "[diesel exhaust] does cause increased tumors in multiple species, multiple tissue sites, multiple routes of exposure. So I think that issue in my mind is fairly straightforward." [BSC Tr. at 388].

NTP's own evaluation of the animal inhalation studies of ETS concedes that "attempts to produce lung cancer in experimental animals by exposing them to tobacco smoke [have been] largely unsuccessful." [1998 ETS Draft, p. 47].

The studies of experimental animals cited by NTP included the following:

- Witschi 1995 - "exposure to tobacco smoke had no effect on pulmonary tumor incidence or tumor multiplicity." [1998 ETS Draft, p. 48].
- Finch 1996 - zero tumor incidence in the smoke-exposed mice. [1998 ETS Draft, p. 49].
- Witschi 1997 - tumor incidence and multiplicity increased in smoke exposed mice but authors concede that "the usefulness of our animal model for the study of human tobacco-smoke induced lung cancer remains to be established." [Witschi 1997, p. 584].

More than half of the studies of experimental animals were completely ignored by NTP. Interestingly, the studies that NTP ignored did not produce tumors in experimental animals:

- von Meyerinck 1989 – The only histopathologic changes observed were hyperplasia and metaplasia of the epithelium covering the dorsal nasal turbinate bones in the rats. These effects were reversible within 90 days. There were no histopathologic changes observed in the hamsters.

- Coggins 1992 – there was no detectable biologic activity in rats exposed either to realistic ETS particulate concentrations (0.1 $mg/m^3$) or extreme ETS particulate concentrations (1 $mg/m^3$). Only minor biologic activity in the nasal organ was observed by the authors in the group of rats exposed to highly exaggerated ETS particulate concentrations (10 $mg/m^3$).

- Coggins 1993 – the authors obtained the same results reported above in Coggins, 1992.

- Haussmann 1998a – The only dose-dependent histopathologic changes observed by these authors were slight reserve cell hyperplasia in the anterior part of the nose and hyperplastic and metaplastic epithelial changes in the larynx. However, the authors also reported that all histopathologic changes reverted to sham control levels following a 42-day postinhalation period.

- Haussmann 1998b – these authors concluded that, for histopathologic changes, pulmonary inflammation, or oxidative DNA damage, there was little indication of progression or occurrence of new effects beyond those observed in the 90-day inhalation study reported by Haussmann, 1998a, discussed above.

As pointed out in the written and oral comments of Dr. Glenn Millner and Dr. Chris Coggins, NTP effectively ignored all negative animal data in favor of data from a problematic animal model (*i.e.*, the strain A/J mouse) for application to human carcinogenicity. [BSC Tr. at 195-197; Christopher R.E. Coggins, Ph.D. 1998 written submission to NTP; Glenn C. Millner, Ph.D. 1998 written submission to NTP]. The strain A/J mouse has problematic applicability to humans for the following reasons: (1) the strain A/J mouse is highly susceptible to spontaneously occurring lung tumors, (2) there is no human equivalent of the benign mouse lung adenoma, and (3) EPA recently

determined that strain A mouse data were inadequate to conclude that a chemical was a potential human carcinogen in humans. [Glenn C. Millner, Ph.D. 1998 written submission to NTP].

Dr. Bingham concluded that the consistently positive animal studies for diesel exhaust were in direct contrast to the generally negative studies of environmental tobacco smoke: "[compared to diesel exhaust] we don't have any animal studies with environmental tobacco smoke." [BSC Tr. at 422]. Dr. Yamasaki sought to explain away the lack of positive results by suggesting that the animal model used in ETS studies was inadequate -- oddly without acknowledging that the same animal model consistently yields tumors from inhalation of diesel exhaust. [BSC Tr. at 186-187].

### 4. NTP attempted to shield from scrutiny its listing decisions for diesel exhaust and ETS

In an alarming exercise of parliamentary authority, Chairman Brown squelched the BSC's burgeoning debate on diesel exhaust, comparisons to NTP's decision making process on ETS, and panel members' pleas for consistency:

| | |
|---|---|
| Chairman Brown: | Let's stay away from environmental tobacco smoke. We did that yesterday. |
| Dr. Belinsky: | I only addressed your issue on the epi study as the comparison. No, we don't have as many studies there for environmental tobacco smoke that are published. |
| Chairman Brown: | I am going to ask that comments from now on be particularly relevant. |
| Dr. Frederick: | Are you getting hungry, Bud? |
| Chairman Brown: | No, I am not getting hungry; I am getting impatient to go on to the next one. Is this particularly relevant? |
| Dr. Mirer: | Yes, it is. |

[BSC Tr. at 422].

### 5. Summary

The inconsistencies of the standards applied by NTP to diesel exhaust and ETS are manifold: 1) the primary chemical constituent analysis (identification of constituents considered carcinogenic by IARC) applied to MS/SS, an improper surrogate for ETS, is equally applicable to, but was absent, for diesel exhaust; 2) the risks reported in the diesel epidemiological studies were greater than those reported for the ETS studies; 3) NTP was concerned about uncontrolled confounding in the diesel exhaust studies but ignored substantial evidence of confounding in the ETS studies; and 4) the NTP record is unequivocal that the diesel exhaust animal studies are consistently positive and the ETS studies are generally negative. In short, NTP's review of, and listing decision for, diesel exhaust cannot be squared with its treatment of ETS.

## B. NTP's review of TCDD is inconsistent with its review of ETS

The BSC also recommended listing 2,3,7,8-tetrachlorodibenzo-p-dioxin ("TCDD") as "reasonably anticipated to be a human carcinogen" in contrast with the BSC's recommended listing of ETS as a "known human carcinogen." Once again, the evidence considered by NTP and comments of the members of the BSC demonstrate that NTP applied inconsistent scientific standards in evaluating ETS and TCDD. If NTP had used the same scientific standards and reasoning in evaluating ETS that it used for TCDD, ETS would have been recommended for a less definitive, not more definitive, listing than TCDD.

### 1. NTP recognized that studies in experimental animals were overwhelmingly positive for TCDD

In contrast to the negative animal data for ETS, NTP identified more than a dozen positive experimental studies of TCDD and carcinogenesis conducted over the past twenty years. [BSC Tr.

at 18]. Tumors have been induced by TCDD in rats, mice and hamsters at multiple sites, including adrenals, hard palate, liver, lung, nasal turbinates, thyroid and tongue:

> "[O]verwhelmingly this evidence suggests that TCDD is a multisite carcinogen . . . TCDD causes tumors in multiple organs and tissues, in multiple species, in multiple strains, in both sexes, by multiple routes of administration in a dose dependent fashion and at very low nontoxic doses, and also after lifetime and even less than lifetime exposures." [BSC Tr. at 19].

Despite the overwhelmingly positive animal data on TCDD, which is not the case for ETS, the BSC still sought additional evidence from human studies before it was willing to conclude that TCDD should be listed as a "known human carcinogen" rather than "reasonably anticipated to be a human carcinogen."

### 2. NTP rejected epidemiological risks for TCDD that are stronger than the epidemiological risks for ETS that were accepted

For TCDD, NTP identified many studies showing a significantly elevated risk of cancer in various sites. NTP described the wealth of epidemiological information published on TCDD. [BSC Tr. at 20]. Characterizing these results, Dr. Masten stated that epidemiological risks for TCDD were in the range of "1.5, 1.3, 1.5, and 1.9, again, . . . . quite weak." [BSC Tr. at 23]. For all cancers combined, NTP identified five out of six studies that found significantly elevated risks, with relative risks ranging from 1.1 to 1.9. For respiratory and/or lung cancer, NTP identified four out of six positive studies with relative risks from 1.4 to 3.2. [BSC Tr. at 22]. For lymphohemopoietic or non-Hodgkin's lymphoma, NTP identified two out of six positive studies with relative risks from 2.2 to 3.7. For bladder or kidney cancer, NTP identified two out of six positive studies, with relative risks from 1.6 to 4.1. [BSC Tr. at 22].

In reviewing the epidemiological data on TCDD, the BSC considered as positive only those

studies with statistically significant relative risks:

> "I had a question for Frank. On these–I guess it goes back to the tables that were given to us by Kim. A lot of the 95 percent confidence intervals for those relative risks go below 1. I guess–I am not an epidemiologist. I am a toxicologist. But I had always had the assumption that if a confidence interval went below 1, then that relative risk wasn't any different from say the unexposed population. So if an epidemiologist can give me a little advice here? . . ."

[Medinsky, BSC Tr. at 78]. Dr. Medinsky's question was never answered by anyone from the BSC or NTP.

Likewise, Dr. Zahm struggled with the problem of nonsignificance in the TCDD epidemiology:

> "The problem is in the data that exists so far it is based on very small numbers. Most of the studies independently aren't statistically significant, although combined it appears that there is something there. It is a struggle. I think based on just the epi data it is limited. It is–you know, it is almost there but it is not quite."

[Zahm, BSC Tr. at 81-82]. Ultimately, the BSC concluded that nonsignificant epidemiological data were not sufficient to justify listing TCDD as a "known human carcinogen."

In contrast, the requirement of statistical significance was abandoned when NTP reviewed the ETS epidemiological studies. If NTP had applied the standard statistical significance criteria (*i.e.*, the lower limit greater than 1.0) to the ETS epidemiological studies, it could only interpret one of the 15 U.S. studies as positive. [1998 ETS Draft, Table 3-1, p. 32]. NTP failed to point out that one of the largest, best-conducted ETS studies, IARC 1998 (Boffetta 1998), with substantial statistical power did not provide results that were positive and statistically significant. In other words, according to the epidemiological standards that NTP used for evaluating the TCDD studies, all but one of the U.S. ETS studies are negative, and cannot establish a causal association between ETS and lung cancer.

Instead, in an unexplained deviation from prior practice, NTP arbitrarily considered any ETS epidemiological study with a relative risk greater than 1.0 to be positive, regardless of statistical significance. Comments by BSC members reflect an agonizing search for some explanation to justify reliance on the weak and inconsistent ETS epidemiologic data:

> "Can you actually just maybe talk a minute about how it might impact epidemiology, because one of the I guess agonies I have with this environmental tobacco smoke data is the really small relative risk associated with the cancer. And so ---"

[Medinsky, BSC Tr. at 207.]

NTP's reviewers downplayed the lack of statistical significance in the ETS studies, and never squarely addressed whether the issue of chance could be excluded as an explanation for any observed association. [Zahm, BSC Tr. at 181-185; Yamasaki, BSC Tr. at 185-187].

### 3. NTP's internal review committees' recommendations on TCDD and ETS were weighed inconsistently

Recommendations of review committees to list TCDD as a "known human carcinogen" were as follows: RG1 - 11 for and zero against (unanimous); RG2 - 8 for and zero against (also unanimous). [BSC Tr. at 30-31]. For ETS, RG1 was similarly unanimous in favor of listing as a "known human carcinogen", but contrary to TCDD, RG2 was split (5 for and 2 against) listing ETS as a "known human carcinogen." [BSC Tr. at 178]. Despite the unanimity of the RG1 and RG2 recommendations for listing TCDD as a "known human carcinogen," the BSC rejected these internal NTP review committee recommendations because it considered the TCDD epidemiological data to be too uncertain. For ETS, the BSC did not address the uncertainties in the epidemiological data and did not apply the same rigorous scientific standards before recommending listing ETS as a "known

human carcinogen."[12]

### 4. Summary

The evidence concerning TCDD and ETS and NTP's treatment of that evidence was different: 1) the risks reported in the TCDD epidemiological studies were greater than those reported for the ETS studies; 2) NTP was concerned about statistical significance with respect to TCDD, but considered every study with a risk greater than 1.0 as positive for ETS, regardless of statistical significance; 3) the studies in experimental animals are overwhelmingly positive for TCDD but generally negative for ETS.

Overall, the scientific evidence presented to NTP is stronger for TCDD than for ETS, yet NTP recommended ETS for a more definitive listing standard. If NTP had evaluated ETS consistently with the standards used in evaluating TCDD, then ETS would have been recommended for a less definitive standard than TCDD. In short, NTP's review of and listing decision regarding TCDD cannot be squared with its treatment of ETS.

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[12]During the session on alcoholic beverage consumption, the BSC recognized the importance of facilitating complete and open debate of all dissenting views on substances being considered for listing. In particular, Dr. Kim Hooper, a member of the BSC, sought to ensure that the BSC had adequately addressed the dissenting opinions expressed in NTP's internal review committee RG1. [BSC Tr. at 163]. The issues raised by the dissenting RG1 member were discussed extensively by the BSC. [BSC Tr. at 163-168]. In contrast, when the BSC considered ETS, the issues raised by the dissenters were ignored. There was virtually no discussion of dissenting views during the ETS session. There was no mention of the dissenting voices on NTP's own internal review committees. NTP failed in its obligation to consider openly and completely the concerns expressed by its own internal review committees.

## V. NTP BASES ITS CONCLUSIONS ON UNRELIABLE REPORTS THAT ARE VACATED AND/OR SUPERSEDED

### A. EPA 1992 cannot be used as a basis for NTP's listing of ETS as a known human carcinogen

#### 1. EPA 1992 was vacated by a United States district court

Throughout its 1998 ETS Draft, NTP places heavy reliance on the U.S. Environmental Protection Agency's 1992 Report on Environmental Tobacco Smoke. However, on July 17, 1998, a federal district court vacated EPA's 1992 Report that sought to classify ETS as a known human carcinogen. *Flue-Cured Tobacco Co-Op et al. v. EPA*, 4 F. Supp. 2d 435 (M.D.N.C. 1998) (attached). The court rejected EPA's methodology and analysis of the ETS data on both scientific and procedural grounds. In addition, the court found that EPA repeatedly had violated the standards of objectivity that should be applied in reviewing scientific evidence.

Reynolds previously pointed out to NTP some of the reasoning in the federal court's decision. [September 18, 1998 letter from Mary E. Ward to C.W. Jameson]. Additionally, some of the oral presentations during the December 2-3 meeting of the BSC referenced the Court's decision to vacate the EPA report. (Gori, BSC Tr. at 223). NTP has not responded to any of these points, nor has NTP provided any justification for its continued reliance on the now vacated EPA report.

The federal district court articulated many reasons for vacating the EPA 1992 report:

- In this case, EPA publicly committed to a conclusion before research had begun; excluded industry by violating the Act's procedural requirements; adjusted established procedure and scientific norms to validate the Agency's public conclusion, and aggressively utilized the Act's authority to disseminate findings to establish a *de facto* regulatory scheme intended to restrict Plaintiff's products and to influence public opinion. In conducting the ETS Risk Assessment, EPA disregarded information and made findings on selective information; did not disseminate significant epidemiological information; deviated from its Risk Assessment Guidelines; failed to disclose

important findings and reasoning; and left significant questions without answers. EPA's conduct left substantial holes in the administrative record. While so doing, EPA produced limited evidence, then claimed the weight of the Agency's research evidence demonstrated ETS causes cancer. (4 F. Supp. 2d at 465-466).

- Using its normal methodology and its selected studies, EPA did not demonstrate a statistically significant association between ETS and lung cancer. This should have caused EPA to reevaluate the inference options used in establishing its plausibility theory. A risk assessment is supposed to entail the best judgment possible based upon the available evidence. [Legal citation omitted.] Instead, EPA changed its methodology to find a statistically significant association. (4 F. Supp. 2d at 463).

- The record and EPA's explanation to the court make it clear that using standard methodology, EPA could not produce statistically significant results with its selected studies. (4 F. Supp 2d at 462).

- The studies EPA selected did not include a significant number of studies and data which demonstrated no association between ETS and cancer. (4 F. Supp. 2d at 463).

- Since Chapter 2 found ETS and MS [mainstream smoke] not sufficiently similar, Chapter 3 found them similar, and Chapter 6 found them dissimilar, EPA apparently used a different risk assessment methodology for each chapter .... The court is faced with the ugly possibility that EPA adopted a methodology for each chapter, without explanation, based on the outcome sought in that chapter. ... Use of cigarette equivalents analysis may have lead to a conclusion that ETS is not a Group A carcinogen. (4 F. Supp 2d at 460).

- EPA's study selection is disturbing. First, there is evidence in the record supporting the accusation that EPA "cherry picked" its data. Without criteria for pooling studies into a meta-analysis, the court cannot determine whether the exclusion of studies likely to disprove EPA's *a priori* hypothesis was coincidence or intentional. Second, EPA's excluding nearly half of the available studies directly conflicts with EPA's purported purpose for analyzing the epidemiological studies and conflicts with EPA's Risk Assessment Guidelines. ... In conducting a risk assessment under the Act, EPA deliberately refused to assess information on all aspects of indoor air quality. (4 F. Supp. 2d at 461).

Because the EPA Report has been vacated by a United States district court, NTP, as an

agency of the federal government, cannot continue to rely on it as a basis for listing ETS in its Ninth Report on Carcinogens. NTP has offered no justification for its continued reliance on this defective and vacated report. At the very least, NTP must address the critical failings in EPA's analysis of ETS. These points were not addressed in NTP's 1998 ETS Draft, or in the BSC meeting in December.

The EPA report's fundamental flaws and shortcomings have been described by many organizations, scientists, and in previous written and oral comments to NTP. Nonetheless, the 1998 ETS Draft adopts the EPA's conclusions without performing the slightest, let alone a critical, reassessment or reanalysis of the data considered by EPA. By relying on the conclusions reached by the EPA report rather than the evidence and data underlying the report, NTP's 1998 ETS Draft promulgates EPA's faulty analysis and methodology.

### B. CEPA 1997 cannot be used as a basis for NTP's listing of ETS as a known human carcinogen

NTP places heavy reliance on the review of ETS and lung cancer conducted in 1997 by the California Environmental Protection Agency ("CEPA"). Similar to NTP's wholesale adoption of EPA 1992, NTP adopts CEPA's conclusions without performing a critical reassessment or reanalysis of the data considered by CEPA. In its perfunctory reliance on the conclusions reached in CEPA 1997, NTP has abdicated its legal responsibility to conduct its own assessment of the evidence on ETS and carcinogenicity. In essence, NTP has recycled a previously recycled version of a vacated and discredited review of the ETS epidemiology.

### 1. CEPA 1997 uses the deficient and vacated EPA 1992 report as a baseline for its analysis

CEPA 1997 relies on the EPA 1992 report as the baseline for its assessment of ETS and lung cancer. In its 1997 review, CEPA sought to determine whether the post-1991 epidemiological literature on ETS was consistent with the conclusions previously reached by EPA. This procedure is invalid for at least two reasons. First, the underlying statistical methodology is not valid. The proper procedure is to determine whether all the data, considered as a whole, are consistent with the standard null hypothesis of no increase in risk (RR=1.0). Had CEPA performed this standard test, CEPA would have concluded that the U.S. data are consistent with no increase in risk. Instead, CEPA turned the scientific process on its head. Based on the U.S. EPA report, CEPA established a nonstandard "null" hypothesis that the true relative risk is 1.19, attempted and failed to reject this new hypothesis using the limited post-1991 data, and declared that the post-1991 data are consistent with a risk level of RR=1.19. CEPA left unspoken the fact that these data are also consistent with a relative risk of 1.0. CEPA's procedure is invalid because it inappropriately places the burden on the post-1991 data to "prove the negative." In other words, CEPA makes the outrageous demand that the new data have sufficient negative impact to reject a contrived "null" hypothesis of elevated risk. This is not, and has never been, accepted practice. Second, even had the statistical methodology been valid, a federal district court subsequently vacated the relevant sections of the EPA report, obliterating the baseline for CEPA 1997. If CEPA's baseline no longer exists, then the premise on which CEPA's analysis rests no longer exists, and CEPA 1997 cannot be considered a valid assessment of the data on ETS and carcinogenicity.

As discussed previously, the conclusions reached in EPA 1992 are misleading and based on

flawed and deficient analyses. As a result, the conclusions of CEPA 1997 are likewise misleading and based on flawed and deficient analyses.

### 2. Contrary to CEPA 1997, the post-1991 epidemiological studies do not support listing ETS as a known human carcinogen

Essentially, CEPA is a review of five post-1991 epidemiological studies of ETS and lung cancer. CEPA could not have reached its conclusion that ETS is causally associated with lung cancer based on a review of these five post-1991 studies. Nonetheless, NTP accepted uncritically CEPA's 1997 conclusions and included sections nearly verbatim from CEPA 1997 in the 1998 ETS draft.

The data presented in the five post-1991 studies contradict the conclusions reached by EPA, CEPA, and NTP:

- Brownson 1992 is a negative study. The most reliable data in the Brownson study -- the direct respondents -- show no increase in risk for spousal or workplace exposure, including in the highest exposure groups. [William J. Butler, Ph.D. 1998 written submission to NTP; BSC Tr. at 212-214].

- The published Fontham 1994 report is unreliable because of flaws in the study design and interpretation. Moreover, when properly analyzed, even the flawed Fontham data shows no association between reported adult ETS exposure and lung cancer risk. [William J. Butler, Ph.D. 1998 written submission to NTP; BSC Tr. at 214-215].

- Kabat 1995 has important design improvements over many earlier studies. Regarding their results, the investigators stated, "[T]he pattern of odds ratios shows little indication of an association between ETS and lung cancer in non-smokers."

- Stockwell 1992 found no statistically significant increased risks for spousal ETS and lung cancer and no risk at all for workplace exposure, despite inadequately addressing confounding and bias. Moreover, the submitted analysis of Ronald Marks, Ph.D. shows no consistent associations between ETS and lung cancer. [Ronald G. Marks, Ph.D. 1998 written submission to NTP; Paul S. Levy, Ph.D. 1998 written submission to NTP; BSC Tr. at 198-199; 224-227].

- Cardenas 1997, a large prospective cohort study based on ACS II, found no

> statistically significant increased risks for lung cancer for males or females. Moreover, Dr. Marks' analysis shows that the only consistent associations for lung cancer among nonsmokers were for dietary variables. [Ronald G. Marks, Ph.D. 1998 written submission to NTP; BSC Tr. at 225].

In previous written comments to NTP, Reynolds provided citations to scientific evidence that supports each of these points. In addition, these points were explained to the BSC on Dec. 2-3, 1998 by Dr. William J. Butler, Dr. Ronald G. Marks, Dr. Paul S. Levy, and others. NTP has an obligation to consider and respond to (1) Dr. Butler's re-analysis of Fontham and Brownson and (2) Dr. Marks' analysis of Brownson, Stockwell, and ACS II (Cardenas 1997).

### C. IARC 1986 does not support NTP's listing of ETS as a known human carcinogen

In 1986, IARC concluded that studies of ETS and lung cancer, at that time, were compatible either with an increased risk or the absence of risk:

> Several epidemiological studies have reported an increased risk of lung cancer in nonsmoking spouses of smokers, although some others have not. In some studies, the risk of lung cancer in nonsmokers increased in relation to the extent of spouses' smoking. Each of the studies had to contend with substantial difficulties in determination of passive exposure to tobacco smoke and to other possible risk factors for the various cancers studied. The resulting errors could arguably have artefactually depressed or raised estimated risks, and, as a consequence, each is compatible either with an increase or with an absence of risk. [IARC 1986, p. 308].

IARC 1998 (Boffetta 1998) has done nothing to change that very basic conclusion, and, in fact, reinforces the conclusion reached by IARC 1986. IARC 1998 (Boffetta 1998) is one of the two largest studies ever conducted to test the hypothesis of an association between ETS and lung cancer among nonsmokers. IARC 1998 supports the conclusion of IARC 1986 that it is not possible, given the nature of the epidemiological evidence on ETS and lung cancer, to conclude that ETS is, or is

not, a human carcinogen. Important findings from IARC 1998 include:

- Overall adulthood relative risks are all weak and nonsignificant.
- Misclassification bias properly handled would decrease the already minuscule relative risks.
- Childhood ETS risks were consistently negative and statistically significant.

[Richard A. Carchman, Ph.D. 1998 Written Comments to NTP; Stephen B. Sears, Ph.D. 1998 Written Comments to NTP; BSC Tr. at 209-212].

## VI. NTP'S REVIEW PROCESS FOR ETS VIOLATES FUNDAMENTAL FAIRNESS

The process for preparing NTP's Reports on Carcinogens includes multiple levels of review. Continuing opportunities for public comment and participation are supposed to be an integral part of the process. *SOCMA v. Secretary, Department of Health and Human Services*, 720 F. Supp. 1244 (W.D. La. 1989). Public participation in NTP's review process was ostensibly encouraged in the Federal Register notices issued by NTP regarding substances being considered for listing in the Ninth Report on Carcinogens. Despite this encouragement and ostensible commitment to reasoned and complete debate, NTP's actual policies and procedures had the effect of stifling public participation and discouraging real public debate. During the December 2-3, 1998 meeting of the BSC, Chairman Brown's introductory remarks emphasized "that there is a limit of five minutes on the formal comments." [BSC Tr. at 14]. Chairman Brown offered the following reason for limiting formal comments to five minutes: "understanding that there are some 35 folks who would like to make public comments, which if we are going to be able to leave here by 5 o'clock tomorrow afternoon it is absolutely necessary that we stay within that five minutes." [BSC Tr. at 14-15]. NTP unreasonably and unfairly limited public debate concerning the carcinogenicity of eleven different substances, especially considering the multitude of complex issues of carcinogenicity for substances

as controversial as alcoholic beverages, ETS, diesel exhaust, and TCDD. NTP offered no reason to justify the discussion of so many substances in these two days. NTP's arbitrary and unreasonably short time limits foreclosed any possibility of actual scientific debate.

NTP has a policy that limits the number of presentations before the BSC. NTP's policy prohibits each interested party from making more than a single presentation. The practical effect of this limitation is to discourage, rather than encourage, public participation in NTP's BSC Meetings. It is unreasonable for an interested party to expect to engage the BSC or have any persuasive impact in a single five minute presentation. NTP's policy that limited one presenter per interested party is contrary to the Federal Register Notice issued by NTP when it solicited public participation for the December 2-3, 1998 BSC Meeting. [63 *Fed Reg* 68783, December 14, 1998]. In the Federal Register Notice, NTP placed no limitation on the number of presenters that interested parties could sponsor at the meeting of the BSC.

During the BSC Meeting, a member of the panel argued that NTP should restrict its consideration of evidence to only published data. [BSC Tr. at 238]. Although there may be some justification for precluding the introduction and consideration of new non-peer-reviewed data for listing decisions by NTP, it is entirely unreasonable to preclude critical analyses of existing published studies, especially studies on which NTP places heavy reliance. In addition, restricting its analysis only to published data would be contrary to NTP's obligation to consider all relevant evidence.

Some of the most critical data and analyses presented to NTP included unpublished analyses by Dr. William J. Butler and Dr. Ronald G. Marks. Independently, these two scientists conducted original analyses on some the largest studies of ETS and lung cancer (*i.e.*, Brownson 1992, Fontham

1994, Stockwell 1992, ACS II (Cardenas 1997)). Their analyses call into serious question the conclusions reached by NTP concerning the proper interpretation of the results from these studies. For NTP to restrict the evidence to published data is unreasonable, especially when the analyses strike at the core of NTP's epidemiological basis for recommending that ETS should be listed as a "known human carcinogen."

## VII. NTP IS OBLIGATED TO CONSIDER ALL EVIDENCE PLACED IN THE RECORD

NTP's conclusions regarding carcinogenicity in humans or experimental animals must be based on scientific judgment, with consideration given to all relevant information, (8th Report on Carcinogens 1998 Summary, p. 2). Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects or other data relating to mechanism of action, and other factors that may be unique to a given substance. (8th Report on Carcinogens, p. 2).

NTP's review process with respect to ETS demonstrates that it has not considered all relevant information. Countless studies, analyses, and data have not been considered by NTP. Instead, NTP seeks to piggyback onto reviews of the ETS literature conducted by other governmental entities, rather than conduct a complete review of the data themselves. Nowhere in NTP's description of its review process and criteria for listing substances does it allow wholesale reliance on other incomplete, outdated, or vacated reviews of the scientific literature.

## VIII. CONCLUSION

For the reasons discussed above, NTP should reject the recommendations of RG1, RG2, and the BSC concerning listing ETS as a "known human carcinogen." ETS should not be included in NTP's Report on Carcinogens, Ninth Edition.